great detail. Vary does not teach an amplification but merely an elongation which employs a single primer (called a probe by Vary; see column 3, line 54, "during the elongation step."). See also Vary Figs. 3A and 3B which show use of a single primer to synthesize only a bottom strand (non-AN). Thus Vary fails to teach "amplifying" as employed in the claimed invention.

Second, the claimed method requires that the primer have "a 5' portion which is identical in sequence to all or part of a probe on a solid support." The rejection asserts that column 7, lines 26-30 of Vary contains such a teaching. Vary's teaching, however, appears inapposite.

> Additionally, the probe P contains a binding segment BS nearer to its 5' end which can be homopolymeric (*e.g.*, poly-dC, poly-rA, or poly dG) or can be a defined sequence (*e.g.*, of viral origin) not expected to be present in the sample nucleic acid.

The binding segment BS of Vary is not defined in this excerpt. However, it is defined at column 7, lines 43-49 (emphasis added):

> The reaction mixture is then contacted by an immobilized polynucleotide IP (or an immobilizable polynucleotide which is subsequently immobilized) having a sequence complementary to binding segment BS of probe P to cause the elongated hybrid to bind selectively thereto and form the bound elongated hybrid BEH shown in Fig. 3B.

Thus rather than teaching a primer and immobilized probe with an identical portion, as required by the claimed invention, Vary teaches a primer and probe which are complementary.

Thus Vary does not anticipate the invention of claims 1, 5, and 7 because it fails to teach at least two elements of the claimed invention.

The Rejection of Claims 2-4, 6, 8, and 10-16 Under 35 U.S.C. §103

Brown, Maniatis and Hames are combined with the primary reference Vary to allege obviousness of claims 2-4, 6, 8 and 10-16. This rejection is respectfully traversed.

Brown and Maniatis are cited as teaching 3' labeling using terminal transferase, Brown is cited as teaching fluorescent labels, Hames is cited as teaching enzyme labeling of DNA. Brown is also cited as teaching comparing fluorescent label at known locations on a solid support to determine the presence of a mutation. Brown is also cited as teaching high density nucleotide arrays.

None of the cited secondary references remedies the deficiencies of Vary with regard to the crux of the invention. None of the prior art teaches a method in which a tag (5' portion) is used on a primer for allele specific amplification in which the tag is "identical in sequence to all or part of a probe on a solid support." No piece of prior art hints at such a method. No combination of prior art suggests such a method. Therefore, the Patent and Trademark Office has failed to make a *prima facie* case that the claimed invention (as defined by all of its elements) would have been obvious over the prior art.

Withdrawal of the rejection is therefore proper.

The Rejection of Claim 9 Under 35 U.S.C. §103

Claim 9 requires the use of two primer pairs which 3' terminate in distinct nucleotides, and whose 5' tags are distinct. Thus each amplification product of alleles A and B will hybridize to distinct locations on the solid support.

Vary, Brown, and Okayama are combined to attempt to render the claim unpatentable. However, as demonstrated above Vary has some glaring deficiencies as a reference. Vary fails to teach tags (5' portions of primers) which are identical to probes on solid supports. Vary fails to teach amplification with two primers. These two failures combine to eviscerate the rejection. If one uses a tag as claimed (identical in sequence to the probe) and fails to amplify but only elongates, one would produce elongation products which will not hybridize to the probes on the solid support, whether or not the target polymorphism is present in the sample. The tags require second strand

synthesis to produce binding partners for the immobilized probes. Okayama is cited as teaching use of two primers pairs. Contrary to the assertion of the Office Action, it would not have been obvious to combine Okayama's exponential amplification with Vary's linear elongation reaction. The Office Action asserts rapidity and specificity would motivate the combination. The Office Action has not shown or explained the source of the expectation of increased rapidity and specificity. Nevertheless, even if one could combine the two teachings properly, *arguendo*, they still do not teach all of the limitations of the claimed invention. Okayama teaches no tags (5' portions of primers). Vary teaches tags, but they have the wrong complementarity for the claimed invention.

The combination of references asserted comes up short. The rejection should be withdrawn.

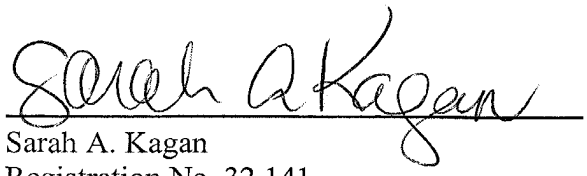
The Rejection of Claims 14 and 15 Under 35 U.S.C. §103

Claims 14 and 15 recite the use of beads and a microtiter dish, respectively, as the solid support in the method of claim 1. Lockhart is combined with Vary to allege obviousness. If Lockhart merely teaches beads and microtiter dishes, then the deficiencies of Vary as an anticipatory reference will remain. In fact, Lockhart is only cited to show that beads and dishes were known as solid supports for binding polynucleotides. Thus this combination of references even if it were properly made would fail to make a *prima facie* case of unpatentability.

None of the prior art suggests the claimed invention, whether alone, or taken in groups. The present invention thus appears to be a fresh idea, different from all cited prior art. It merits a patent. Withdrawal of all rejections is requested. Please speedily pass this application to allowance.

Respectfully submitted,

Date: August 17, 2000

By: 

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